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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,524	09/09/1998	TOSHIO SONE	SPO-103	2300

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EXAMINER
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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/142,524	Sone et al
Examiner	**Art Unit**
Marianne DiBrino	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *7/12/01, 3/6/02 and 5/22/02*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 4-6, 13, 17, and 31-48* is/are pending in the applica

4a) Of the above, claim(s) *35-47* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4-6, 13, 17, 31-33, and 48* is/are rejected.

7) ☒ Claim(s) *34* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) filed 7/12/01 based on parent Application No. 09/142,524 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's amendments filed 7/12/01 (Paper No. 24) and 3/6/02 (Paper No. 26) and Applicant's response filed 5/22/02 (Paper No. 30) are acknowledged and have been entered.

3. Applicant is reminded that claims 49-66 on pages 3-5 of the amendment filed 7/12/01 have been renumbered as claims 31-48 according to 37 CFR 1.126 because when claims are added, they must be numbered by the Applicant consecutively beginning with the number next following the highest numbered claim previously presented. Applicant is reminded that the amendment after final under 37 C.F.R. 1.116 filed 1/19/01 containing proposed claims 31-48 was not entered.

Claims 1, 4-6, 13, 17 and 31-48 are pending.

4. Applicant's election with traverse of Group I (claims 1, 4-6, 13, 17, 31-34 and 48) is acknowledged.

The basis of the traversal is that there is no undue burden and the patentability of both inventive groups revolves around the patentability of the peptides provided in the invention of Group I and used in the invention of Group II, that if the product is found allowable, then withdrawn process claims will be rejoined, that the instant application is a continuing prosecution application of PCT JP97/00740, and that the parent was examined under unity of invention rules.

Applicant's argument has been considered, but is not deemed persuasive for the following reasons. The USPTO policy formulated based upon In re Ochiai 37 USPQ2d 1127 (Fed. Cir. 1995) and In re Bouwer 37 USPQd 1663 (Fed. Cir. 1996) is to rejoin groups drawn to methods of using a product with the product claims after patentability of the product claims has been determined, and Unity of Invention was broken in the parent case.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 35-47 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP §821.03.

Claims 1, 4-6, 13, 17, 31-34 and 48 are presently being examined.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 4-6 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant specification and claims as originally filed do not support the following limitation:

In claim 4, "site that is cleaved in vivo" because said site does not have to be in between T cell epitopes.

In claim 6, "or immunostimulatory fragments of SEQ ID NO: 1, 2 or 3".

In claim 33, "DRβ1*1501" and "DRβ1*0901".

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 4-6, 13, 17, 31-33 and 48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al (Molecular Immunology, Vol. 31 (13) pp 955-966, 1994, entire document) in view of WO 94/01560 (20 January 1994, pages 1-106) and further in view of Hashiguchi et al (Peptide Chemistry, Volume 33, 1996, pages 409-412) or Komiyama et al (Biochemical and Biophysical Research Communications, Volume 201, 1994, pages 1021-1028) or WO 94/11512, Wallner et al (Allergy, Volume 49, 1994, pages 302-308), Rammensee et al.

Rogers et al teach a peptide-based immmunotherapeutic agent comprising a linear multi-epitope linear polypeptide with different T cell epitopes joined to each other, and wherein the said polypeptide does not substantially react with allergic human IgE, wherein said different T cell epitope regions are derived from two or more different allergen molecules and wherein said polypeptide reacts with peripheral lymphocytes from at least not less than 70% of said population patients sensitive to said allergens (especially Abstract; page 956; Table 2; page 961, column 1, second full paragraph; page 963, column 1, lines 6-9; page 964, column 1, first two full paragraphs; page 964, column 2, lines 24-29 and lines 60-71; page 965, lines 1-2). Rogers et al teach that their approach to a peptide-based immunotherapeutic agent can be generally applicable to the combination of multiple T cell epitope-containing sequences from one or more antigens into a single polypeptide chain, that a single antigen can have multiple T cell epitopes recognized in the atopic human population, and that the polypeptide can also be constructed using T cell epitopes from unrelated antigens or allergens from diverse sources page 964, lines 60-71 and continuing onto page 965, lines 1-2). Rogers et al teach the importance of the human T cell reactivity to individual T cell epitopes being maintained in the said polypeptide agent (especially Abstract and page 961, column 2). Rogers et al teach that making said T-cell epitope-containing peptides which have significantly reduced reactivity with allergic human IgE is a novel and useful therapeutic approach for desensitization to important allergens.

Rogers et al do not teach said immunotherapeutic agent supra wherein the T cell epitope regions are comprise different allergen molecules that are cedar pollen allergens Cry j 1 and Cry j 2. Rogers et al do not teach said immunotherapeutic agent wherein a site that is processed in the antigen-presenting cells is inserted between each of the T cell epitope regions, and wherein said site is an arginine dimer (R-R) or a lysine dimer (K-K), nor wherein the polypeptide molecule comprises at least one T cell epitope restricted by one of HLA class II DR, DQ or DP, nor wherein the T-cell epitope peptides are analog peptides in which one or more amino acid residues of the T-cell epitope peptides are substituted.

The WO 94/01560 document teaches linear polypeptides comprising at least two different T cell epitope regions from Cry j 1 joined to each other which do not substantially react with allergic human IgE (especially Abstract, page 4, lines 17-24, page 13, lines 12-20). The WO 94/01560 teaches that peptides are selected based upon various factors including the

frequency of the T cell response to the peptide in a population of individuals sensitive to the allergens and the strength of the T cell response to the peptide. It also teaches pharmaceutical compositions containing these polypeptides which comprise a sufficient percentage of the T cell epitopes such that at least about 60% of the T cell reactivity of the allergens are included in the composition. WO 94/01560 teaches that charged amino acid pairs such as KK or RR can be introduced between T cell epitope regions and that the resulting peptide is rendered sensitive to capthepsin and/or other trypsin-like enzymes which are involved in processing of T cell epitopes in vivo (especially page 24, lines 5-13). WO 94/01560 teaches peptides comprising at least two regions, each region comprising at least two T cell epitopes of a Japanese cedar pollen protein allergen or comprising epitopes from peptides which are immunologically related (especially page 26, lines 25-31). The WO 94/01560 document also teaches a method for determining which peptides from cry j 1 or another allergen have T cell epitope regions (especially page 27, lines 19-32 and continuing onto page 28, lines 1-5). WO 94/01560 teaches a peptide CJI-22 (211-230) which has the sequence KSMKVTVAFNQFGPNCGQRM (especially figure 13). Said peptide contains an amino acid sequence described in SEQ ID NO: 1, 2 and 3 (underlined) that is immunostimulatory, i.e., "immunostimulatory fragment". WO 94/01560 further teaches a peptide analog or modified peptide in which amino acid residues have been substituted to increase solubility, enhance therapeutic or preventive efficacy or to enhance ex vivo or in vivo stability, i.e., to increase resistance to proteolytic degradation in vivo or to increase shelf life ex vivo, to modify immunogenicity or reduce allergenicity or to modify reaction with T cell receptors or MHC binding of the T cell epitopes (especially pages 22 and 23).

Hashiguchi et al teach T cell epitopes of Cry j 2.

WO 94/11512 teaches purified Cry j 2 protein, and T cell epitopes thereof, a method of producing the protein and epitopes and a method of identifying T cell epitopes, and the usefulness in treatment, diagnosing and preventing Japanese cedar pollinosis (especially Abstract, page 14, lines 35-36 and continuing onto page 15, lines 1-6 and lines 17-37 and page 16, lines 1-36). WO 94/11512 further teaches a peptide analog or modified peptide in which amino acid residues have been substituted to increase solubility, enhance therapeutic or preventive efficacy or to enhance ex vivo or in vivo stability, i.e., to increase resistance to proteolytic degradation in vivo or to increase shelf life ex vivo, to modify immunogenicity or reduce allergenicity or to modify reaction with T cell receptors or MHC binding of the T cell epitopes (especially pages 13 and 14).

Komiyama et al teach the deduced amino acid sequence of Cry j 2, the second major allergen of Japanese Cedar Pollen, Cry j 1 being the first (especially Abstract and page 1021 and first paragraph of page 1022). Komiyama et al teach that amino acid sequence information for Cry j 2 is useful for the determination of T cell epitopes from that allergen (especially page 1027, lines 3-8). Komiyama et al teach that patients suffering from pollinosis have IgE antibodies

specific for Cry j 1 and Cry j 2 (especially page 1022, lines 7-8) and the usefulness of recombinant Cry j 2 protein for immunotherapy (especially page 1027, lines 8-10).

Wallner et al teach that the diversity of the human population with respect to its HLA haplotype has to be taken into account in defining clinical peptide candidates. Wallner et al teach that permissive interaction between peptides and several HLA alleles probably accounts for the observation that peptides containing the major T-cell epitope of an allergen cause T-cell responses in 80-90% of the allergic population and that clinical peptide candidates therefore have to be designed to cover the diverse HLA haplotype of the allergic patient population.

Rammensee et al teach haplotypes of HLA-DR, DQ and DP and peptides that bind to them, including DRβ5*0101.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a multi-epitope immunotherapeutic agent such as the one taught by Rogers et al with the regions joined to each other via peptide bond using the cryj1 peptides of WO 94/01560 and cry j2 peptides deduced from the teachings of Hashiguchi et al and Komiyama et al or of WO 94/11512, respectively, given the teaching of Rogers et al that a multi-epitope peptide can be constructed using T cell epitopes from allergens from diverse sources. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make T-cell epitope-containing peptides which have significantly reduced reactivity with allergic human IgE for use in desensitization to important allergens, such as treatment of pollenosis caused by Japanese Cedar Pollen, as taught by Rogers et al in order to treat pollenosis. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed a multi-epitope peptide using lysine or arginine dimers that can be introduced between T cell epitope regions to serve as a site that is processed in antigen-presenting cells given the teaching of WO 94/01560. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to enhance processing of the epitopes for presentation by HLA as taught by WO 94/01560. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to create a peptide-based immunotherapeutic agent that contains an epitope restricted by HLA class II molecules such as those taught by Rammensee et al that are frequent in different patient population groups being targeted, as taught by Wallner et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made T-cell epitope peptides that are analog peptides as taught by WO 94/01560 and WO 94/11512 in order to increase solubility, enhance therapeutic or preventive efficacy or to enhance ex vivo or in vivo stability, i.e., to increase resistance to proteolytic degradation in vivo or to increase shelf life ex vivo, to modify immunogenicity or reduce allergenicity or to modify reaction with T cell receptors or MHC binding of the T cell epitopes as taught by WO 94/01560 and WO 94/11512.

During examination, claims are given their broadest reasonable interpretation. Instant claims 1, 4-6, 13, 17 and 31-33 are included in this rejection because it would have been obvious to one of ordinary skill at the time the invention was made: to have made an immunotherapeutic agent that reacts dose-dependently in a population of allergic patients, selected said T cell epitopes that interact with more than one HLA haplotype selected from DP, DQ and DR, particularly given the teaching of Wallner et al supra; to have determined the minimal epitope, i.e., minimum core sequences, for T cell epitopes restricted by particular HLA haplotypes; to have selected epitopes that provide the greatest possible protection. Instant claim 33 is included in this rejection because the HLA-DPA1 and HLA-DQA1 alleles taught by Rammensee et al are variants of *0101, i.e., the serological allele, and one of ordinary skill in the art at the time the invention was made would have been aware that the same peptide might bind the variant. Instant claim 31 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to alter the T-cell epitope peptide to contain no Cys residue in order that no residues be present which could form disulfide bonds.

9. Claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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